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Abstract

People with HIV experience a high prevalence and burden of symptoms throughout their disease trajectory. These have important public and clinical health implications. We aimed to measure: the seven-day period prevalence of symptoms, the most burdensome symptoms, and determine if symptom burden is associated with treatment status, clinical stage and physical performance.

We conducted a cross-sectional study among adult (aged at least 18 years) patients with HIV, attending outpatient care in Kenya. Data was gathered through self-report using the Memorial Symptom Assessment Scale-Short Form (MSAS-SF), file extraction (sociodemographic and clinical data) and through observation using the Karnofsky Performance Scale. Multivariable ordinal logistic regression assessed the association of symptom burden controlling for demographic and clinical variables.

Of the 475 participants approached, 400 (84.2%) participated. Ordinal logistic regression showed that being on HIV treatment was associated lower global distress index (in quartiles) (odds ratio .45, 95% CI .23 to .88; $p=0.019$).

Pain and symptom burden still persist in the era of antiretroviral therapy. Routine clinical practice should incorporate assessment and management of pain and symptoms irrespective of disease stage and treatment status in order to achieve the proposed fourth '90' in the UNAIDS 90-90-90 targets (that is good quality of life).

Introduction and background

Kenya is one of the countries in the sub-Saharan region with a high prevalence of HIV infection. It shares fourth position alongside Mozambique and Uganda in terms of HIV prevalence. UNAIDS estimates that at the end of 2015, there were 1.5 million people living with HIV in Kenya with 5.9% adult prevalence (WHO/UNAIDS, 2015). Kenya has

made positive strides in terms of implementing the 90-90-90 UNAIDS policy. At the end of 2015, 64% of the population were on HIV treatment. Death rate declined from 51,000 in 2010 to 36,000 in 2015.

Despite the availability of HIV treatment to optimise care for people living with HIV (PLWA), multi-dimensional problems still persist. Patients with HIV experience physical, psychological, social and spiritual problems from the point of diagnosis (Simms et al., 2011) within two weeks of diagnosis (Simms et al., 2013) and during treatment (Harding et al., 2006, Harding et al., 2010). Our prior evidence from the UK, South Africa and Uganda have demonstrated a high prevalence and burden of problems in outpatient settings alongside ART (Harding et al., 2010, Namisango et al., 2012, Farrant et al., 2012). These problems have negative effects on the life of the patients (Harding et al., 2012a).

Clinicians and policy makers are increasingly recognising that patient self-reported outcomes are essential to ensure optimal health service access and equity in health status (Dawson et al., 2010). A whole person-centred approach to HIV treatment, care and support is essential to optimise outcomes, and is advocated in global policy for those with any stage of HIV infection and alongside treatment (WHO, 2011). WHO advocates for pain and symptom control in HIV clinical care as essential components within the package of care (WHO, 2011).

The clinical and public health relevance of these problems are demonstrated in the relationship between symptom burden (physical and psychological) and sexual risk taking (Harding et al., 2012b) poor adherence to treatment (Sherr et al., 2008), and viral rebound (Lampe et al., 2010). Symptoms in HIV are present throughout the disease trajectory regardless of CD4 count and stage classification (Peltzer and Phaswana-Mafuya, 2008, Willard et al., 2009). The burden of symptoms has not been carefully examined in terms of its association with clinical staging and treatment status. Symptom burden in HIV is associated with poor drug adherence and poor quality of life (Harding et

al., 2010, Hughes et al., 2004, Brechtel et al., 2001, Rosenfeld et al., 1996), We therefore conducted a cross-sectional study on living with HIV in order to examine the seven day prevalence of physical and psychological symptoms among PLWH and determine if symptom burden was associated with treatment status and clinical stage of illness, to inform the development of self-management interventions in HIV and new clinical guidelines in the management of pain and symptoms. Given wider roll out of effective treatments, the paucity of recent data on pain and symptoms among PLWH, and the increasing focus on patient-reported outcomes and quality of life, this study is timely to ensure that HIV treatment and care services can respond to patient needs and concerns.

Methods

We did a cross-sectional study using self-reported data, file extraction and observer ratings. Participants were included if they were adult (aged at least 18 years) patients with documented HIV diagnosis, and aware of their diagnosis. Participants were recruited at an HIV outpatient care facility (Bomu hospital) in Mombasa, Kenya. Bomu hospital offers a wide range of services for HIV patients such as counselling and testing, inpatient and outpatient treatment of HIV for both adults and children. The hospital also provides medical services for patients with other medical conditions such as lung disease, diabetes, malaria. Ethical approval was obtained from the Kenyan Medical Research Institute (KEMRI/RES/7/3/1).

Procedures

The researcher used a random number table each day to select the first patient to approach in the patient outpatient queue. Each patient approached had the information sheet read aloud. They were then asked to make an informed decision to take part in the study. If they were willing to take part, they were asked to sign the consent form. The researcher subsequently approached every consecutive patient. The researcher recorded

the number of acceptances and refusals daily, in order to calculate the response rate. A payment of \$5 was made for patient expenses in relation to participation in the study, and a drink/fruit snack was offered. The researcher is a highly experienced Kenyan researcher who has worked in this setting with this population on several previous studies of people living with HIV (Lowther et al., 2012, Lowther et al., 2015b), and is fluent in local languages.

Sample size calculation

Sample size calculation was based on HIV prevalence in Kenya. UNAIDS data report that 1.5 million Kenyans are infected with HIV (95% CI 1.3m, 1.6m) (WHO/UNAIDS, 2015). With 95% confidence, 5% margin of error, and a response distribution of 50% for any outcome we estimated that 385 were required to determine prevalence of any outcome. We therefore recruited 400 to allow for any non-completers.

Data collection

The researcher extracted CD4, treatment status for HIV and TB from patient's records. The researcher administered questionnaires to gather self-reported data in a private space at the clinic. All responses were recorded by the researcher and answers given verbally by participants. This helped to reduce any potential response bias by mixing self-completion and researcher-completion. Data were collected using tools previously implemented/validated in African in HIV populations. The tools were:

1. The Memorial Symptom Assessment Scales Short Form (MSAS-SF) was used to assess symptoms. MSAS-SF measured the prevalence and burden of physical and psychological symptoms in the past seven days (Chang et al., 2000). MSAS-SF has three subscale indices of physical symptom distress (MSAS-PHYS), psychological symptom distress (MSAS-PSYCH) and global distress index (MSAS-GDI), each has a score range of 0-4. It is applicable in a wide range of conditions, and enables comparison between conditions (Harding et al., 2010). It was recently used in symptom cluster studies among HIV

patients conducted in Uganda and South Africa (Moens et al., 2015, Namisango et al., 2015).

2. Demographics, socioeconomic status using Demographic and Health Survey (DHS) (Gwatkin et al., 2007), using variables such as house construction, possession of items, fuel supply, and water source. These variables were used to calculate the wealth of the participants. The wealth quintile variable was created in line with the methods of DHS (Gwatkin et al., 2007). We used factor analysis with principal component analysis to create a continuous variable which was then converted into quintile. DHS has previously been used in HIV research in sub-Saharan Africa (Lowther et al., 2012, Harding et al., 2014).

3. The Karnofsky Performance Status (KPS). This is an observer-rated scale widely been used in HIV population (Namisango et al., 2015). It is used to assess the level of physical function of the patient, rated on a scale of 0-100, with 0 corresponding to no physical function (death) and 100 corresponding to maximum independent functioning (Mor et al., 1984). The Karnofsky Performance Scale was previously used in a symptom cluster study among HIV patients in Uganda (Moens et al., 2015, Namisango et al., 2015).

Data analysis

Data was entered into a spreadsheet with a unique identifier for each patient. The spreadsheet was converted into Stata version 14 dataset (StataCorp, 2015).

The prevalence of each symptom and distress associated with each symptom was tabulated. All MSAS-SF subscales were computed and calculated based on the methods of the MSAS-SF. For the presence of physical symptoms they were computed as follows: 0.8 'no distress at all', 1.6 'a little bit', 2.4 'somewhat', 3.2 'quite a bit' and 4.0 'very much'. For the presence of psychological symptoms they were computed as follows: 1 'rarely' 2 'occasional' 3 'frequently' and 4 'almost constantly'. Most distressing symptoms were calculated, these were symptoms scored using the worst two categories

of burden (i.e., causes 'quite a bit' or 'very much' distress for physical symptoms and 'frequently' or 'almost constantly' for psychological symptoms). Individuals under these two worst categories were regarded as experiencing high distress.

MSAS-GDI, MSAS-PHYS and MSAS-PSYCH scores were not normally distributed. They were therefore converted into quartiles (MSAS-GDI) and quintiles (MSAS-PHYS and MSAS-PSYCH). CD₄ count were converted into textures We used this classification based on CD₄ count cut-offs and the risks of opportunistic infections in line with a study conducted in Ethiopia (Damtie et al., 2013).

The KPS scores were skewed and were therefore converted into binary variable with two groups: (1) with a score of $\leq 80\%$, unable to carry normal activity or work (2) with a score of $>80\%$ ability to carry normal activity and work. This was based on a study by Peus et al (2013) who recommended to use an algorithm with a minimum of two and a maximum of three variables to facilitate an adequate and efficient evaluation of the KPS (Péus et al., 2013). Descriptive statistics were used to profile the demographic, socioeconomic and clinical characteristics of participants.

The dependent outcomes were global distress index (MSAS-GDI), physical symptom distress (MSAS-PHYS) and psychological symptom distress (MSAS-PSYCH). Covariates were demographic variables (age, gender, education, and wealth in quintiles), clinical variables (HIV stage, CD₄ count, TB treatment: yes/no, ART treatment: yes/no and KPS). Initially we conducted a univariate analysis for demographic, and clinical variables. We then conducted adjusted analysis for demographic variables falling within less than 25% p value (Altman, 1991). Clinical variables (HIV treatment status, CD₄ count, HIV clinical stage, TB treatment status) were forced into the multivariate models regardless of the outcome of the univariate analysis. This is because these are confounding clinical variables frequently associated with HIV outcomes. We were interested in risk factor modelling not just prediction. Furthermore, after we retained clinical variables we produced richer models and assumptions met. Studies have shown that researchers can

return confounding variables as long as sample sizes are larger because correct retention increases with sample size (Bursac et al., 2008). Physical symptoms such as pain occur due to HIV illness or HIV treatment (Marcus et al., 2000, Vogl et al., 1999), peripheral neuropathy due to TB infection and treatment (Chen et al., 2013, Evans et al., 2011, Ellis et al., 2010) CD4 count (Aouizerat et al., 2010, Richardson et al., 2009) and clinical stage (Martin et al., 1999, Dobalian et al., 2004, Nair et al., 2009) are frequently associated with HIV illness. We conducted a 'brant' test of parallel regression assumption. A non-significant test statistic provided evidence that the parallel regression assumption were met. All cases with missing data were excluded from the models.

Results

Table 1 presents the demographic and clinical characteristics of the participants. Of the 475 participants approached, 400 (84.2%) participated. The mean age was 39.4 years (SD 9.9), range 18-74 years. The majority were females (n=280, 70%). Just over half of the sample (n=213, 53.25%) as attended primary school, and just over a quarter (n=113, 28.25%) attended secondary school.

Treatment variables

Treatment variables are presented on table 1. Most of the patients were currently on ART (n=366, 91.5%), with (n=61, 15.64%) also on TB treatment. The mean CD4 count was 393.7(SD=238.2). Most of the participants were on stage 3 of HIV infection (n=343, 85.75%). The majority of the patients disclosed their status to someone (n=373, 93.25%). In relation to the physical performance score (KPS) n=298 (74.5%) were above 80%.

Symptoms reported

The mean symptom distress subscale indices were: global distress index (GDI) 13.34 (SD=10.06), physical symptom distress (PHYS) 12.52 (SD= 9.88) and psychological

symptom distress (PSYCH) was 8.44 (SD=7.22). The ten most prevalent symptoms are presented on table 2. Pain was the most prevalent symptom reported (n=244, 61%), followed by feeling sad (n=235, 58.75%). Manifestations of fatigue were also most common, such as feeling drowsy (55.25%), difficulty in concentrating (55%) and lack of energy (55%). Other most prevalent symptoms were problems with sexual activity (54.24%), worry (49.5%), numbness (46.25%), feeling irritable (45%) and hunger (42.75%).

The ten most distressing symptoms (worst two categories reported as “quite a bit” or “very much” for physical symptoms and “frequently” or “almost constantly” for psychological symptoms) were problems with sexual activity (71.43%), hunger (69.58%), feeling nervous (66.86%), feeling sad (63.83%), feeling irritable (62.73%), worry (59.59%), suicidal (53.45%), changes in the skin (53.22%), lack of sleep (53.15%), and feeling drowsy (49.77%).

Predictors of symptom prevalence and distress

Univariate and multivariate ordinal logistic regression models were constructed as shown on tables 3, 4 and 5.

ART treatment, age, gender and KPS were significantly associated with global distress index (see table 3). Being on ART was associated with lower (better) global distress index (odds ratio .45, 95% CI .23 to .88; $p=0.019$). Women experienced worse global distress index (odds ratio 2.97, 95% CI 1.95 to 4.52; $p<0.001$). Age predicted lower global symptom distress (odds ratio .98, 95% CI .96 to 1.00; $p=0.048$). Participants with KPS >80% had lower (better) global distress index (odds ratio .32, 95% CI .20 to .50; $p<0.001$).

Gender and KPS were associated with physical and psychological symptom distress. Women reported higher (i.e. worse) physical symptom distress (odds ratio 2.28, 95% CI 1.52 to 3.41; $p<0.001$). Participants with KPS scores of >80% had lower physical (i.e.

better) symptom distress (odds ratio .28, 95% CI .18 to .45; $p < 0.001$) (see table 4).

Likewise on table 5, women experienced higher (i.e. worse) psychological symptom distress (odds ratio 3.17, 95% CI 2.11 to 4.78; $p < 0.001$). Patients with KPS scores of $>80\%$ were associated with lower (i.e. better) psychological symptom distress (odds ratio .43, 95% CI .28 to .67; $p < 0.001$).

In summary gender and KPS were associated with all the symptom subscales (GDI, PHYS and PSYCH).

Discussion

Data from this study shows that people with HIV attending outpatient clinic reported high prevalence of physical and psychological symptoms. Compared to other studies conducted in Uganda using the same measure in similar populations, our results are comparable in terms of the most prevalent symptoms (Wakeham et al., 2010, Namisango et al., 2013), although the prevalence was much higher in the Ugandan studies for pain (Wakeham et al., 2010), feeling drowsy, lack of energy (Namisango et al., 2013, Wakeham et al., 2010), numbness of feet and hands (Wakeham et al., 2010). However the prevalence was lower in another Ugandan study compared to our study for pain and difficulty concentration (Namisango et al., 2013). Interestingly problems with sexual activity were rated the top most distressing symptom in all the studies. Other most distressing symptoms were feeling sad, worry, pain and lack of energy. Compared with similar work done in the UK, similar symptoms were reported and most prevalent were lack of energy, worry, problems with sexual activity and pain (Harding et al., 2010). However, prevalence rates were higher in the UK study. The prevalence and burden of symptoms reported in our study are similar to those reported in a review by Solano and colleagues (Solano et al., 2006).

Pain prevalence was high and among the most burdensome physical symptoms in our study. Several studies in HIV (Huang et al., 2013, Kolawole Wasiu and Alakija Kazeem,

2011, Richardson et al., 2009, Kimball and McCormick, 1996, Wakeham et al., 2017) and cancer (Huang et al., 2013) population have reported high prevalence of pain alongside ART. Several authors have reported that pain and other physical and psychological symptoms persist in HIV alongside ART (Harding et al., 2010, Lowther et al., 2014).

Being female and KPS >80% were associated with all the three MSAS subscales. Similarly a cross-sectional study conducted in Uganda reported that KPS>70% were associated with symptom burden of each MSAS subscale (Namisango et al., 2013). In our study being female was associated with higher physical, psychological and global distress and burden. Likewise a multi-country study in sub-Saharan Africa and an American sample concluded that females experienced higher symptom burden (Potter et al., 2003, Koole et al., 2016), however in the Ugandan study, being male was associated with psychological symptom distress (Namisango et al., 2013).

Our results show that being on ART was associated with lower global distress index scores, however there was no significant association with physical and psychological distress measures. Similarly a recent longitudinal study conducted in Uganda among HIV patients using the same tool concluded that symptom prevalence and distress indices reduced after ART was initiated (Wakeham et al., 2017). However, our results are at odds with previous cross-sectional study conducted in UK and Uganda that reported that ART treatment is not associated with any symptom distress measure (Namisango et al., 2013, Harding et al., 2010).

Our findings show that prevalence and distress of symptoms were not associated with CD₄ count and clinical stage. Similarly a cross-sectional study conducted in Uganda in the same population reported that CD₄ count and clinical stage were not associated with symptom burden (Wakeham et al., 2010). This is contrary to findings from a heterogeneous HIV infected American population that reported higher pain prevalence among patients with low CD₄ count (Richardson et al., 2009, Aouizerat et al., 2010) and higher pain prevalence among patients with advanced HIV infection (Martin et al., 1999,

Dobalian et al., 2004, Nair et al., 2009) and higher symptom burden at stage IV (Namisango et al., 2013). Our findings therefore are important to inform policy that pain and symptom management is critical at each stage of the infection and regardless of CD₄ count.

The current study shows that hunger was one of the top ten prevalent symptoms and top five most distressing symptoms. This requires holistic patient-centred care and more attention because hunger may result in poor drug adherence (Harding et al., 2010). A recent longitudinal study reported that prior to starting ART hunger prevalence was 43%, and it remained the same after one year, suggesting that hunger does not decrease with ART (Wakeham et al., 2017). In an African context hunger is due to poverty and long distance to access the clinic including long waiting time to meet the doctor (Hardon et al., 2007). A recent multi-country study conducted in Zambia, Uganda and Tanzania concluded that besides ART, not having enough food were the cause of hunger, and this led to poor drug adherence (Koole et al., 2016). ART provision and food integration should be encouraged in Kenya. A systematic review reported that provision of food supplements alongside ART reduces poor drug adherence (Singer et al., 2015).

Study strengths and limitations

We used questionnaires validated in local population and researcher administered the questionnaires. Our study provides novel data on symptom prevalence and burden among HIV patients through self-report. Our study had a response rate of 84.2 %.

This study however has some limitations. This data was cross-sectional therefore, we can only determine associations. Data on viral load was missing in the patient records, although it is notable that previous studies have shown that higher viral load is associated with poor physical function (Nieves-Lugo et al., 2017), high burden of symptoms and low CD4 count (Richardson et al., 2002, Cox et al., 2018).

Our novel data informs care delivery to support the guidelines for providing pain and symptom management for patients with HIV.

Conclusion

The prevalence and burden of physical and psychological symptoms persist in HIV particularly among women. The burden of hunger needs attention and further work to identify strategies to deal with this symptom in order to prevent poor drug adherence and attrition from HIV care.

HIV clinical care is evolving from a medical model for delivery of effective treatments to person-centred care that addresses patient-reported outcomes. Recent evidence suggests that not only is pain more prevalent among PLWH compared to matched controls, but is associated with poorer function and lost days of employment (Sabin et al., 2018).

If we are to achieve the proposed fourth “90” in the UNAIDS 90x90x90 targets, i.e. good quality of life for people living with HIV (Lazarus et al., 2016), then careful assessment of pain and symptoms must be a priority. This requires the replication of simple interventions to deliver person-centred HIV outpatient care (Logie and Harding, 2005b, Lowther et al., 2018a, Lowther et al., 2018b, Lowther et al., 2016, Lowther et al., 2015a), strategies to ensure pain relieving drugs are available in pharmacies and are prescribed (Logie and Harding, 2005a), and that low cost, effective interventions such as pain self-management for people living with HIV are delivered (Nkhoma et al., 2018, Nkhoma et al., 2015).

Importantly, our data highlight the importance of self-reported outcomes from diagnosis until the end of life. Routine clinical practice should incorporate assessment and management of pain and symptoms irrespective of disease stage and treatment status, given their high prevalence and burden.

Conflict of interest

No conflicts of interests to declare.

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